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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Steven H. Krawczyk

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GILEAD SCIENCES INC
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FOSTER CITY, CA 94404

EXAMINER

BALASUBRAMANIAN, VENKATARAMAN

ART UNIT

PAPER NUMBER

1624

MAIL DATE

DELIVERY MODE

09/02/2008

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/566,819	Applicant(s) KRAWCZYK, STEVEN H.	
	Examiner /Venkataraman Balasubramanian/	Art Unit 1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 08 May 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-24 is/are pending in the application.
- 4a) Of the above claim(s) 1-10, 19, 21 and 23 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 11-18, 20, 22 and 24 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Claims 1-24 are pending.

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

- I. Claims 1-10, 11-18 (part), 19, 20 (part), 21, 22 (part), 23 and 24 (part) drawn to purine compound of formula shown in claim 1 and purine compound of formula shown in claim 11 wherein the nucleobase is purine, composition and method of use, classified in class 544, subclass 264, class 514, subclass 263.3.
- II. Claims 11-18, 20, 22, 24, drawn to compound of formula shown in claim 11 wherein the nucleobase is pyrimidine, namely pyrimidine compound, composition and method of use, classified in class 544 subclass 315, class 514, subclass 269
- III. Claims 11-18, 20, 22, 24, drawn to compound of formula shown in claim 11 wherein the nucleobase is other than purine or pyrimidine, namely pyrimidine compound, composition and method of use, classified in class 544, 546, 548 etc., subclasses various, class 514, subclasses various depending upon the choice of nucleobase which include indole, pyrrole, imidazopyridine etc. If this group is elected applicants should also elect a specific nucleobase for examination.

The inventions are distinct, each from the other because of the following reasons:

Invention I , II and III are independent and distinct from each other because they are directed to structurally dissimilar compounds that lack common core, namely, purine versus pyrimidine versus various nucleobases which include various triazines, fused triazine, azapurines, azapyrimidines, indoles, imidazopyrimidines, imidazopyridines etc to name a few. Consequently, the groups have different classifications and require separate prior art searches. They can be made and used independently. Art which may render obvious or anticipate one of the groups would not necessarily do the same for the other group. For example, prior art cited in the Information Disclosure Statement (see for example those cited in the IPER) may not be applicable to all the above groups. Each can support a patent as the compounds of each group are capable of being utilized alone not in combination with other members listed in the Markush group.

In addition, it is necessary to classify and search all the controlling cores generically embraced in Group I, II and III. Such a search of all controlling cores would be a serious search burden.

Restriction for examination purposes as indicated is proper because all these inventions listed in this action are independent or distinct for the reasons given above and there would be a serious search and examination burden if restriction were not required because one or more of the following reasons apply:

- (a) the inventions have acquired a separate status in the art in view of their different classification;
- (b) the inventions have acquired a separate status in the art due to their recognized divergent subject matter;

- (c) the inventions require a different field of search (for example, searching different classes/subclasses or electronic resources, or employing different search queries);
- (d) the prior art applicable to one invention would not likely be applicable to another invention;
- (e) the inventions are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a invention to be examined even though the requirement may be traversed (37 CFR 1.143) and (ii) identification of the claims encompassing the elected invention.

The election of an invention may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected invention.

If claims are added after the election, applicant must indicate which of these claims are readable upon the elected invention.

Should applicant traverse on the ground that the inventions are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

During a telephone conversation with Alan Kutzenco on 5/8/2008 a provisional election was made without traverse to prosecute the invention of Group II claims 11-18, 2, and 24. Affirmation of this election must be made by applicant in replying to this Office action. Claims 1-10, 19, 21, 23 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 11-18, 20, 22 and 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

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1. Recitation of "a composition" in claims 11-18 renders these claims indefinite as a composition requires more than one ingredient.
2. Recitation of "with a pharmaceutical composition or formulation comprising an effective amount of a compound of claim 11" in claims 20 and 22 renders these claims indefinite as claim 11 is not recited as a compound claim.
3. Recitation of "a pharmaceutical composition comprising an effective amount of a compound of claim 11" in claim 24 renders claim 24 indefinite as claim 11 is not recited as a compound claim.
4. Recitation of +N(OR) as a choice for Y¹ and Y² renders claim 11 and its dependent claims indefinite as a trivalent nitrogen cannot have a charge.
5. Recitation choices for R¹ through R⁸ renders claim 11 and its dependent claims indefinite as these groups, including ammonium, carry a charge without any counterion. The structural make-up of compounds with these groups remains unknown.
3. The same is true for "carboxylate", which is -COO⁻. This also lacks a counterion. Likewise for sulfate.
4. The term "sulfamate" and "sulphonate" are unclear. For example, the latter would be -OSO₂R, but what is R?
5. Recitation of C₁-alkenyl, C₁-alkynyl in claim 11 renders claim 11 and its dependent claims indefinite as alkenyl and alkynyl cannot have C₁. Such groups require a minimum of 2 carbons. See e.g. definition of R.
6. The last X¹ choice is identical to the preceding one. It is not clear what is intended and what the difference between the two is. Deletion is suggested.

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The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 20 and 22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of HIV infection does not reasonably provide enablement for prevention of the symptoms or effects of HIV. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant claims 20 and 22 are drawn to, besides treatment, prevention of symptoms or effects of HIV infection. Instant claims, as recited, are reach through claims. A reach through claim is a claim drawn to a mechanistic, receptor binding or enzymatic functionality in general format and thereby reach through a scope of invention for which they lack adequate written description and enabling disclosure in the specification.

In the instant case, based on the inhibition of HIV reverse transcriptase by the instant compounds, instant claims reaches through inhibiting and treating any or all diseases in general and thereby they lack adequate written description and enabling disclosure in the specification.

More specifically, in the instant case, based on the mode of action of instant compounds as inhibitor of reverse transcriptase, based on limited assay, it is claimed that preventing HIV infection for which there is no enabling disclosure.

The instant compounds are disclosed to have HIV reverse transcriptase inhibitory

activity and it is recited that the instant compounds are therefore useful in preventing HIV infection for which applicants provide no competent evidence. It appears that the applicants are asserting that the embraced compounds because of their mode action as HIV reverse transcriptase inhibitor that they would be useful for preventing said HIV infection. However, the applicants have not provided any competent evidence that the instantly disclosed tests are highly predictive for preventing HIV for the intended host.

To prevent” actually means to anticipate or counter in advance, to keep from happening etc. (as per Webster's II Dictionary) and there is no disclosure as to how one skilled in the art can reasonably establish the basis and the type of subject to which the instant compounds can be administered in order to have the “prevention” effect. There is no evidence of record, which would enable the skilled artisan in the identification of the people who have the potential of becoming afflicted with the inflammatory and or immune disease(s) or disorder(s) claimed herein.

That a single class of compounds can be used to prevent HIV infection in general embraced in the claims is an incredible finding for which applicants have not provided supporting evidence. Moreover, HIV infection is very difficult to treat and despite the fact that there are many drugs including several reverse transcriptase inhibitors, HIV protease inhibitors and integrase inhibitors, none of them have found to prevent the said disease.

Furthermore, instant claims clearly acknowledge drug resistance and evolution of drug resistance strains. Hence, it is clear that these drugs cannot prevent the HIV infection as embraced in the instant claims.

Note substantiation of utility and its scope is required when utility is “speculative”, “sufficiently unusual” or not provided. See *Ex parte Jovanovics*, 211 USPQ 907, 909; *In re Langer* 183 USPQ 288. Also note *Hoffman v. Klaus* 9 USPQ 2d 1657 and *Ex parte Powers* 220 USPQ 925 regarding type of testing needed to support in vivo uses.

Next, applicant's attention is drawn to the Revised Interim Utility and Written Description Guidelines, at 64 FR 71427 and 71440 (December 21, 1999) wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed method of preventing solely based on the inhibitory activity disclosed for the compounds. Prior art search in this area only lend support for treating the HIV infection not preventing HIV infection. See Sarafianos et al., *Current Opinion in Structural Biology*, 14, 716-730, 2004.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention: Therapeutic use of the compounds in preventing HIV infection that require reverse transcriptase inhibitory activity.

2) The state of the prior art: Prior art in the related area teach treating HIV infection

using reverse transcriptase inhibitors and or protease inhibitors but not preventing the said infection. See Sarafianos et al., cited above. Again, the fact that drug resistance strains evolve is clear-cut indication that prevention is not possible these drugs.

3) The predictability or lack thereof in the art: Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use for preventing HIV infection based on the said mode of action. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, “the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved”. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

4) The amount of direction or guidance present and 5) the presence or absence of working examples: Specification has no working examples to show preventing HIV infection and the state of the art does not lend support for preventing HIV infection using reverse transcriptase inhibitors.

6) The breadth of the claims: The instant claims embrace preventing HIV infection due to inhibition of reverse transcriptase.

7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use, for the reasons stated above.

Thus, factors such as “sufficient working examples”, “the level of skill in the art” and “predictability”, etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical

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nature of the invention, the unpredictability of enzyme-inhibitor interactions in general, and the lack of working examples regarding the activity of the claimed compounds towards preventing HIV infection, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was 'filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 11, 12 and 24 are rejected under 35 U.S.C. 102(e) as being anticipated by Hardee, WO 2005/020885.

Hardee teaches several compounds to treat viral infection such as SAR, which include instant compounds. See pages 14-56 for various preferred embodiments and pages 64-74 for examples. See pages 141-214, Table I for 1360 compounds. Especially see compound 175.

Claims 11, 12, 14 and 24 are rejected under 35 U.S.C. 102(e) as being anticipated by Chand, WO 2004/106350.

Chand teaches several compounds to treat several viral infections, which include instant compounds. See page 3, formula I and note the definition of A, B, Y, Z, Z' and W. Note with the given definition of these variables when B is cytosine or uracil, i.e. a pyrimidine base, the compounds and composition taught by Chand include instant compound and composition. See pages 3-33 for various preferred embodiments and process of making these compounds. See pages 33-36 for examples of species which include instant pyrimidinyl species. See third, fourth, fifth and sixth species shown in page 33 and last but four species on page 34.

Claims 11, 12 and 24 are rejected under 35 U.S.C. 102(b) as being anticipated by Vemishetti, US 5,591,852.

See entire document. Especially, Scheme II, Scheme III and examples 1-22.

Claims 11, 12 and 24 are rejected under 35 U.S.C. 102(b) as being anticipated by Guanti et al., Tetrahedron, 51(35), 9737-9746, 1995.

Guanti teaches several nucleoside analogues, which include instant compounds. See entire document. Especially, Scheme I, Scheme II and various examples shown in pages 9740-9745.

Claims 11, 12, 20, 22 and 24 are rejected under 35 U.S.C. 102(b) as being anticipated by Casara et al. Bioorganic & Medicinal Chemistry Letters, 5(12), 1275-1280, 1995.

Casara teaches several nucleoside analogues for treating HIV, which include instant compounds, composition and method of use. See entire document. Especially, Schemes 1-3, Table I and Table 2 for various examples and the activity of the compounds.

Claims 11, 12 and 24 are rejected under 35 U.S.C. 102(b) as being anticipated by Kim et al., J. Med. Chem., 33, 1797-1800, 1990.

Casara teaches several nucleoside analogues for treating HSV, which include instant compound and composition. See entire document. Especially, Schemes II, compound 15.

Claims 11, 12 and 24 are rejected under 35 U.S.C. 102(b) as being anticipated by Holy et al., Collection of Czechoslovak Chemical Communications, 54(9), 2470-2501, 1989; CA 113: 41170, 1990. CAPLUS Abstract provided.

Holy teaches several nucleoside analogues which include instant compound and composition. See entire document for various compounds.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims, 11-18 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hardee, WO 2005/020885.

Hardee teaches several compounds to treat viral infection such as SAR, which include instant compounds. See pages 14-56 for various preferred embodiments and pages 64-74 for examples. See pages 141-214 , Table I for 1360 compounds. Especially see compound 175.

Hardee differs in not exemplifying all compounds generically embraced therein. However, Hardee teaches equivalency of those compounds taught with those generically claimed. Hence, it would be obvious to one trained in the art to make all compounds taught by Hardee with the guidance of those exemplified and expect these compounds have the same use taught therein.

Claims, 11-18 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chand, WO 2004/106350.

Chand teaches several compounds to treat several viral infections, which include instant compounds. See page 3, formula I and note the definition of A, B, Y, Z, Z' and W. Note with the given definition of these variables when B is cytosine or uracil, i.e. a

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pyrimidine base, the compounds and composition taught by Chand include instant compound and composition. See pages 3-33 for various preferred embodiments and process of making these compounds. See pages 33-36 for examples of species which include instant pyrimidinyl species. See third, fourth, fifth and sixth species shown in page 33 and last but four species on page 34.

Chand differs in not exemplifying all compounds generically embraced in compound of formula I. However, Chand teaches equivalency of those compounds taught with those generically claimed. Hence, it would be obvious to one trained in the art to make all compounds taught by Chand with the guidance of those exemplified and expect these compounds have the same use taught therein.

Conclusion

Any inquiry concerning this communication from the examiner should be addressed to Venkataraman Balasubramanian (Bala) whose telephone number is (571) 272-0662. The examiner can normally be reached on Monday through Thursday from 8.00 AM to 6.00 PM. The Supervisory Patent Examiner (SPE) of the art unit 1624 is James O. Wilson, whose telephone number is 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAG. Status

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information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-2 17-9197 (toll-free).

/Venkataraman Balasubramanian/

Primary Examiner, Art Unit 1624